REMARKS

Applicants submit a revised Preliminary Amendment in response to the Office Action dated September 10, 2002. The original Preliminary Amendment, filed by Applicants on June 24, 2002, was determined to be a "bona fide, non-responsive amendment " by the Examiner. Specifically, "[t]he amendment filed 6/24/02 to claims 1 and 6 is not consistent with originally filed claims 1 and 6." Applicants have therefore amended claims 1 and 6 to be consistent with originally filed claims 1 and 6.

No new matter is being added by the foregoing amendments. Claims 1 and 6 are amended to more distinctly point out the patient population on whom the claimed invention is practiced. Specifically, Applicants have added the phrases "in need of such treatment" and "in need of such lowering" to claims 1 and 6 respectively. Support for these amendments can be found throughout the Specification as filed, page 2, lines 5-17. Additionally, Applicants have cancelled claims 2-5, 7, 9-17, and 19-30 and added claims 32 – 55, without prejudice. The latter represent the subject matter of former claims 27 - 28, rewritten in independent and proper dependent format.

Applicants have amended the specification to correct typographical errors. Applicants have also submitted an abstract as required by 37 C.F.R. 1.72(b).

Reconsideration of the application in view of the above amendments and the following remarks is requested.

Rejections under 35 U.S.C. 102(b)

The Examiner has rejected claims 1, 3, 6-8, 10, 13-15, 18, 20 and 27-29 as being anticipated by Moller et al. (Clin. Science, Vol. 75, pp. 345-350, 1988), (Moller). According to the Examiner:

> "Moller discloses the use of mixed SSTR-2/SSTR-5 agonist (e.g., SMS 201-995 or somatostain-14 for the treatment of hyperlipidemia in which the reference clearly demonstrates the lowering of triglycerides levels...and blood glycerol levels. Thus the reference clearly anticipates the method of treating

> hyperlipidemia by administering a therapeutically effective amount of a type-5 selective somatostatin agonist...to a patient to reduce triglyceride and glycerol levels in the blood of said patient and to a pharmaceutical formulations thereof. (see Office Action, page 5, lines 8-14).

Applicants disagree. Claims 1 and 6 are directed to a method of treating hyperlipidemia comprising administering a therapeutically effective amount of a somatostatin type-5 receptor (SSTR-5) agonist. An SSTR-5 agonist is clearly defined in the Specification as:

> ...a compound which (1) has a high binding affinity (e.g., Ki of less than 5 nM or preferably less than 2 nm or less than 1 nm) for SSTR-5 (e.g. as defined by the receptor binding assay described below) and (2) decreases lipid levels...(page 9, lines 10-17).

Moller discloses the administration of SMS-201-995. Applicants refer to WO 96/35950, which was cited by Applicants in their Information Disclosure Statement filed November 9, 1999 and by the Examiner in the March 28, 2001 Office Action. This reference shows that SMS-201-995 exhibits Ki values of 9.14 and 7.0 for rat and human SSTR-5 respectively (see Tables I and II on pages 14 and 17). Thus, SMS-201-995 does not fall within Applicants' definition of an SSTR-5 agonist as set forth in the application, because the SSTR-5 binding constants observed for SMS-201-995 are not below 5nM. Therefore, Moller does not disclose the claim element of administering a therapeutically effective amount of an SSTR-5 agonist.

Applicants have amended claims 1 and 6 to include the phrases "in need of such treatment" and "in need of such lowering" respectively. This language is introduced to clarify that the patient being treated by the claimed methods has specifically been identified as one in need of treatment of hyperlipidemia or in need of lowering of blood triacylglycerols, glycerol or cholesterol. The identification criteria are described in the Specification, e.g., page 2, lines 5-17.

Moller describes a study wherein five "healthy subjects" (page 345, column 2, line 35) were given a test meal (following an overnight fast) and then injected with a dosing solution containing SMS 201-995. Blood levels of e.g., blood glycerols and serum trigycerides were monitored in each of the five patients. The objective of the study was "to examine the effects of

SMS 201-995 on gastrointestinal transit time and absorption of fat and carbohydrates in normal man" (emphasis added, page 347, column 1, lines 19-22).

While the study revealed that a lowering of blood glycerol and triglycerides was observed in the five healthy subjects, Applicants submit that the protocol and data described by Moller does not rise to the level of anticipating the methods of claims 1 and 6, that is, patients in need of such treatment. First, the subjects of the Moller study were merely volunteers and were not selected on the basis of their personal or family medical history. There is no indication that they were identified or solicited on the basis of a predisposition towards hyperlipidemia or high plasma lipid levels in general. In fact, other than body weight, no other medical data concerning the subjects is disclosed. Second, the final statement in the Moller study is as follows:

> "Whether these findings would be reproduced in patients treated chronically with the drug is unknown" (page 350, column 1, lines 49-50).

The above-quoted passage from Moller demonstrates that the administration of SMS 201-995 produced the above physiological effects in a specific segment of the population only, i.e., "healthy subjects." It therefore cannot be construed as a method of treating hyperlipidemia in a patient in need of such treatment or as a method of lowering blood triacylglycerols, glycerol or cholesterol in a patient in need of such lowering. In other words, Moller fails to describe the elements of "a method of treating hyperlipidemia in a patient in need of such treatment" (i.e., claim 1) or "a method of lowering acylglycerols, glycerol or cholesterol in a patient in need of such lowering" (i.e., claim 6). Since Moller does not anticipate claims 1 and 6, it also does not anticipate pending claims 8 and 18, which depend from claim 6. Applicants therefore respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. 103(a)

The Examiner has rejected claims 1-30 under 35 U.S.C. 103(a) as being unpatentable over Moller et al. (Clin. Science, Vol. 75, pp. 345-350, 1988), (Moller) in view of WO 96/35950 or Degrado.

Applicants disagree. These three references, whether considered individually or together, do not teach the claimed invention. In particular, these references do not teach the use of a compound with a Ki of less than 5 nM for the somatostatin type-5 receptor to treat hyperlipidemia within a patient population specifically in need of treatment for such a disorder. Therefore, Applicants submit that the Examiner has not established a *prima facie* case of obviousness, because the claim limitations of Applicants' invention are not taught by this prior art.

Conclusion

The foregoing amendments are made without waiver or prejudice to Applicants' right to pursue any cancelled subject matter in a later or continuing patent application claiming benefit of this application.

Applicants believe that the instant application, as amended, is in condition for allowance. Prompt and favorable action is earnestly solicited.

Attached is a marked-up version of the changes being made by the current amendments.

Applicant asks that all claims be examined. Enclosed is a $1,450.00 check for the Four-Month Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: February 10, 2003

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 5, line 3 has been amended as follows:

Definitions of "somatostatin type-5 receptor agonist" and "somatostatin type-5 receptor selective agonist" will be given below. A therapeutically effective amount depends upon the condition being treated, the route of administration chosen, and the specific activity of the compound used and ultimately will be decided by the attending physician or veterinarian (e.g., [:] 5 g/day and 5 mg/day). In one embodiment, the somatostatin agonist is administered to the patient until the patient's lipid levels (e.g., glycerol, tracylglycerols, or cholesterol) decrease. In another embodiment, the somatostatin agonist is administered for the lifetime of the patient.

Paragraph beginning at page 17, line 4 has been amended as follows:

The effect of chronic treatment with BIM-23268 on plasma lipids was examined in an obese animal model, the fatty (fa/fa) Zucker rats (Bray, G., Federation Proceedings 36:q48-153 (1977)) (purchased from Harlan-Olac, Bicester, Oxon, U.K.). Eleven male fatty Zucker rats weighing about 450 grams were randomly divided into 2 groups and their initial body wights recorded. The animals were housed in pairs in a normal 12 hour light/dark cycle at 20 ["] = 21C and fed a standard laboratory rat diet (Beekay rat and mouse diet, Bantin & Kingman, Hull, Humberside, U.K.) overnight *ad libitum*.

In the claims:

Claims 2-5, 7, 9-17, and 19-30 have been cancelled.

Claims 1 and 6 have been amended as follows:

-- 1. (Amended) A method of treating hyperlipidemia in a patient in need of such treatment due to diabetes mellitus, hypothyroidism, uremia, nephrotic syndrome, acromegaly, obstructive liver disease, dysproteinemia, drugs or genetic disorders said method comprising

administering a therapeutically effective amount of a somatostatin type-5 receptor agonist to said patient.

6. (Amended) A method according to claim 1, of lowering the amount of triacylglycerols, glycerol, or cholesterol in the blood of a patient in need of such lowering. --